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LETTER TO THE EDITOR

On comparing different devices of inhalation products

Dear Editor,

I read with interest the article by van Noord et al.[1] to see how the difficult task of inhalation product comparison had been addressed. The authors investigated non-inferiority versus the existing reference product and concluded that Tiotropium 5 μg SMI is comparable with Tiotropium 18 μg HH in terms of efficacy, pharmacokinetic and safety. In contrast to the authors' opinion, I think that the data presented by the authors show that Tiotropium 5 μg SMI is superior in lung deposition and efficacy, inferior in safety and not comparable to Tiotropium 18 μg HH.

Firstly, the study was insensitive to compare devices because Tiotropium 10 μg SMI provided an additional 0.001 L improvement in the primary efficacy variable (trough FEV_1) compared with the improvement observed with Tiotropium 5 μg SMI over placebo (0.126 L). It means that doubling the dose (100% increase) produces only a 0.8% increase in response. This illustrates that 5 and 10 μg of SMI were on the flat part of the dose–response curve. Then, any dose would have looked similar. Obviously, this is not demonstration of similarity; this is simply demonstration of an insensitive study design that is unable to distinguish between two adjacent doses. In this respect, I would like to highlight once more[2,3] that it is essential to learn that to be methodologically valid any comparison between inhalation devices has to be done as a comparison of the dose–response curves of both devices[4,5] by means of the calculation of the relative potency[6–8] in a patient population and study design able to show differences between adjacent doses. Interestingly, despite the insensitivity of the trial the difference between Tiotropium 5 μg SMI and 18 μg HH (0.029 L) was statistically significant (the 95%CI of the difference does not include the zero value in table 2a).

Secondly, the pharmacokinetic results based on urinary data were able to show a much better sensitivity since doubling the dose produced double systemic exposure, which illustrates the usefulness of pharmacokinetic comparisons. The amount excreted in urine reflects the amount of drug deposited in the lungs since the fraction absorbed through the gastrointestinal tract is negligible for Tiotropium. Therefore, the urinary data is able to confirm what we already knew: a product with the same formulation and device but with double strength should show double lung deposition. However, the pharmacodynamic endpoint was unable to provide any information on such a simple comparison. Plasma systemic exposure is more informative that urinary excretion data. Unfortunately, the blood sampling times in these studies (0, 10, 60 and 360 min after dosing) were clearly insufficient to obtain a reliable estimate of the concentration - time profile. The plasma concentration-time profile does not only provide information about the lung deposition when the gastrointestinal absorption is negligible, but also provide information on the pattern of deposition, since the deeper the deposition the shorter t_{max} and the higher C_{max}.[9–11] From a pharmacokinetic point of view a 26% difference in urinary excretion is not demonstrative of equivalence or bioequivalence. On the contrary, it suggests that a 4-μg dose of SMI should be compared with 18 μg of HH. With respect to safety, on one side this study was not powered to compare the safety profile. Therefore, the inability to detect differences in the safety profile cannot be considered as demonstration of similarity. The inability to reject the null hypothesis does not support the validity of the null hypothesis. On the other side, the systemic exposure with Tiotropium 5 μg SMI was higher than with Tiotropium 18 μg HH. Therefore, it has to be assumed that Tiotropium 5 μg SMI posses a worse systemic safety profile, even if this small study was not able to detect it.

This represents the personal opinion of the author and does not necessarily represent the views or policy of the Spanish Agency for Medicines and Health Care Products.

Conflict of interest

None, the author is clinical assessor of a European Regulatory Agency and fulfills the conflict of interest policy of EMEA.

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